National Institute for Health and Care Excellence

Health Technology Evaluation

Obicetrapib and obicetrapib–ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID6519]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Menarini	A. Menarini Farmaceutica Internazionale SRL have no comment to add. We align with the proposed routing through single technology appraisal.	Thank you for your comments.
	HEART UK	Single technology appraisal, this topic is appropriate as an additional lipid lowering treatment, particularly when intolerance to other medications exists/patients usually require more than one lipid lowering treatment to reduce their levels to current national targets/some may not be able to access some medications as they do not meet certain prescription criteria i.e. LDL levels.	Thank you for your comments.
	Daiichi Sankyo	N/A	N/A
	Novartis	N/A	N/A

Section	Stakeholder	Comments [sic]	Action
	Primary Care Cardiovascular Society	It is appropriate for NICE to start to evaluate this product.	Thank you for your comment.
	UK Clinical Pharmacy Association	Evaluation of this topic is appropriate, considering the benefit these new therapies could have in those patients needing support with reducing cholesterol. To ensure consistency among evaluations with the other lipid lowering therapies, separate technology appraisals for obicetrapib and obicetrapib/ ezetimibe would be appropriate. It would have a useful place in therapy in patients who struggle with needle-phobia or otherwise reluctant to initiate injectable therapy with inclisiran or a PCSK9i. The combination product of obicetrapib with ezetimibe has a better predicted LDL reduction than bempedoic acid/ ezetimibe combination (50% v 38%).	Thank you for your comment. The 2 interventions will still need to be considered separately, and being appraised in the same evaluation allows for this. Similar instances are where an evaluation considers multiple populations or subgroups.
Wording	Menarini	A. Menarini Farmaceutica Internazionale SRL have no comment to add. We align with the wording used.	Thank you for your comment.
	HEART UK	Should the intervention reflect the population i.e. obicetrapib monotherapy as an adjunct to diet and maximally tolerated lipid modifying therapy?	Thank you for your comment, the wording of the remit states that obicetrapib will be appraised within its anticipated marketing authorisation. The wording of the interventions has been updated to add “with

Section	Stakeholder	Comments [sic]	Action
			maximally tolerated lipid-lowering therapy".
	Daiichi Sankyo	N/A	N/A
	Novartis	N/A	N/A
	Primary Care Cardiovascular Society	No comment	N/A
	UK Clinical Pharmacy Association	Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? Yes	Thank you for your comment.
Timing Issues	Menarini	A. Menarini Farmaceutica Internazionale SRL consider the single technology appraisal planned appropriate to ensure timely patient access to the NHS.	Thank you for your comment.
	HEART UK	Although other treatments are currently available, some people cannot access them and so this medication should be available sooner to add to the current lipid management pathway.	Thank you for your comment. The appraisal has been scheduled into the work programme.
	Daiichi Sankyo	N/A	N/A
	Novartis	Persistently elevated LDL-C remains a major, largely modifiable driver of atherosclerotic cardiovascular disease, yet a substantial proportion of high- and very high-risk patients still do not achieve guideline-recommended LDL-C targets despite the availability of effective therapies. Many patients are undertreated, treated late, or remain above target due to barriers such as	Thank you for your comments.

Section	Stakeholder	Comments [sic]	Action
		therapeutic inertia, sub-maximal statin use, intolerance, limited access to combination therapy, and challenges with long-term adherence. Given the strong, well-established relationship between cumulative LDL-C exposure and cardiovascular events, there is a clear need for greater urgency in LDL-C management: earlier risk identification, more consistent use of maximally tolerated statins, timely escalation to combination and advanced therapies where appropriate, and system-level changes that support proactive, target-driven lipid control. Without a step change in how aggressively and consistently we manage LDL-C, avoidable cardiovascular morbidity and mortality will continue to occur.	
	Primary Care Cardiovascular Society	Outcome data is not yet available for this product. Given the previous data with other medicines in this class the timeline for evaluation will need careful consideration to when outcome data is likely to be available	Thank you for your comments. The company will provide an evidence submission which will include outcomes data for the technologies.
	UK Clinical Pharmacy Association	A timely evaluation of obicetrapib and obicetrapib/ezetimibe would benefit patients. Ascertaining if this medication is part of the lipid lowering toolkit in the UK is important for CVD prevention and treatment options and choice for patients.	Thank you for your comment. The appraisal has been scheduled into the work programme.
Additional comments on the draft remit	Menarini	No additional comment	N/A
	HEART UK	N/A	N/A
	Daiichi Sankyo	N/A	N/A

Section	Stakeholder	Comments [sic]	Action
	Novartis	N/A	N/A
	Primary Care Cardiovascular Society	N/A	N/A
	UK Clinical Pharmacy Association	N/A	N/A

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Menarini	A. Menarini Farmaceutica Internazionale SRL propose the following changes: **<u>Background Information</u>** **Current wording:** "For some people, LDL cholesterol levels may remain above treatment goals despite maximally tolerated lipid-lowering therapy." **Proposed wording:** "For some people, LDL cholesterol levels may remain above treatment goals despite maximally tolerated lipid-lowering therapy. This underscores an unmet need within the current lipid-lowering treatment pathway and highlights the importance of introducing new therapeutic options." In the DaVinci (2021) EU-Wide cross-sectional observational study only 33% of patients achieved their risk-based 2019 LDL-C goal (N=4112),with goal	Thank you for your comments. The background section aims to give a brief overview of the condition and current treatment. Please include these additional details in the company submission.

Section	Consultee/ Commentator	Comments [sic]	Action
		attainment higher among individuals at lower CV risk and lower among those at higher risk. The SANTORINI (2023) European observational study estimated that 73.3% of overall patients included (N=9044) did not achieve their LDL-C lowering goals as per the 2019 ESC/EAS guidelines.	
	HEART UK	N/A	N/A
	Daiichi Sankyo	N/A	N/A
	Novartis	Please amend the bullet point to the following: • "TA733 recommends ~~the PCSK9 inhibitor~~ inclisiran, **a small interfering RNA (siRNA) therapy** as an option for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet in adults, if there is a history of cardiovascular events ~~or~~ **AND** if LDL cholesterol concentrations are persistently 2.6 mmol/l or more, despite maximally tolerated ~~lipid-lowering therapy~~ **statins with or without other lipid-lowering therapies or other lipid-lowering therapies when statins are not tolerated or contraindicated. Inclisiran is supplied under the updated (2025) commercial agreement with NHS England**". Please move the bullet point for TA694 after TA733, given that TA694 is only an option if statins are C/I and if ezetimibe alone doesn't control LDL-C and therefore represent a small subset of the population compared with TA733. Please check the following value/reference:	Thank you for your comments. The bullet wording and ordering has been amended. The following sentence has been removed as the estimate cannot be verified in the primary source: "Around 7.8% of people have primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia". Reference to clinical guidelines has been added.

Section	Consultee/ Commentator	Comments [sic]	Action
		"Around 7.8% of people have primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia". It would also be helpful to refer to the summary of national guidance for lipid management for primary and secondary prevention of cardiovascular disease (CVD), Cardiovascular disease: risk assessment and reduction, including lipid modification (published 14 December 2023). NHS Accelerated Access Collaborative » Summary of national guidance for lipid management	
	Primary Care Cardiovascular Society	None	N/A
	UK Clinical Pharmacy Association	Statins should be included in the background and the role of statins as first line lipid lowering therapy should be emphasised	Thank you for your comment, the role of statins as a first line treatment has been emphasised.
Interventions	Menarini	**Interventions (first row of table)** **Current wording:** • **"**Obicetrapib monotherapy as an adjunct to diet" • "Obicetrapib–ezetimibe fixed dose combination as an adjunct to diet" **Proposed wording:** • "Obicetrapib monotherapy as an adjunct to diet **on top of statins and other LLTs"**	Thank you for your comment. The intervention wording has been amended to include "with maximally tolerated lipid-lowering therapy" for both technologies.

Section	Consultee/ Commentator	Comments [sic]	Action
		• "Obicetrapib–ezetimibe fixed dose combination as an adjunct to diet on top of statins in addition to ezetimibe"	
Population	Menarini	A. Menarini Farmaceutica Internazionale SRL agree that the population is defined appropriately.	Thank you for your comment.
	HEART UK	Clarify if this is for primary and secondary prevention of CVD.	Thank you for your comment. The following wording has been added to the population: "with or without a history of atherosclerotic CVD" to align with the trial data.
	Daiichi Sankyo	N/A	N/A
	Novartis	N/A	N/A
	Primary Care Cardiovascular Society	Is the population defined appropriately? Yes	Thank you for your comment.
	UK Clinical Pharmacy Association	Need to clarify if the intention is to evaluate use in patients with and/or without history of cardiovascular disease	Thank you for your comment. The following wording has been added to the population: "with or without a history of

Section	Consultee/ Commentator	Comments [sic]	Action
			atherosclerotic CVD" to align with the trial data.

Subgroups	Menarini	**Current wording:**
		• "Primary hypercholesterolaemia
		  ○ Heterozygous familial
		  ○ Non-familial
		• Mixed dyslipidaemia
		• Statins contraindicated or not tolerated"
		Proposed wording:
		• "Primary hypercholesterolaemia
		  ○ Heterozygous familial
		  ○ Non-familial"
		A.Menarini Farmaceutica Internazionale SRL request that the scope be simplified to reflect the broader population eligible for treatment and suggest removing the proposed subgroups for the following reasons:
		• Typically the suggested subgroups do not represent distinct treatment populations in clinical trials for novel lipid-lowering agents, including the obicetrapib development programme. Additionally obicetrapib's mechanism (CETP inhibition) is entirely independent of the mechanism of statins (HMG-CoA reductase inhibition).
		• Regarding the statin-intolerance group, due to the mechanism of action, the drug is expected to enhance lipid lowering regardless of whether the background therapy is a statin or another non-statin agent. Presenting separate efficacy and safety data by statin tolerance status would be fragmenting the evidence base. The overall trial population is the most appropriate representation of patients who will receive the drug.
			Thank you for your comments. The subgroup for "statins contraindicated or not tolerated" has been removed. The "mixed dyslipidaemia" subgroup remains in the scope as it is not clear why this should be removed.

Section	Consultee/ Commentator	Comments [sic]	Action
		• The difference in treatment pathways between statin-tolerant vs. statin-intolerant will be reflected via the comparators. Relevant subgroups in terms of risk level, disease progression and/or background will be reflected based on the relevant comparator.	
	HEART UK	This treatment targets LDL receptors so is only effective in those with working LDL receptors. Consider adding a subgroup under 'statins contraindicated/not tolerated' - those who may not meet the criteria for injectables such as PCSK9 monoclonal antibodies (evolocumab/alirocumab) or inclisiran but who are at still at cardiovascular risk.	Thank you for your comment. We have removed the statins contraindicated/not tolerated subgroup. Committee will consider all relevant evidence
	Daiichi Sankyo	The draft scope includes statin intolerant subgroups, whilst obicetrapib has been studied in patients with maximally tolerated lipid modifying therapy. Please clarify how evidence for statin-intolerant populations, inadequately controlled on ezetimibe and bempedoic acid will be derived, and how uncertainty from extrapolation will be addressed in the appraisal.	Thank you for your comment. The statins contraindicated/not tolerated subgroup has been removed. Statin-intolerant populations were not excluded from the clinical trial. The company will address the decision problem in their evidence submission.
	Novartis	N/A	N/A

Section	Consultee/ Commentator	Comments [sic]	Action
	Primary Care Cardiovascular Society	Familial hypercholesterolemia primary prevention	Thank you for your comment, a subgroup for “history of atherosclerotic CVD” has been added.
	UK Clinical Pharmacy Association	These match subgroups in comparator NICE TAs.	Thank you for your comment.

Comparators	Menarini	A.Menarini Farmaceutica Internazionale SRL recommend changing the Comparators section to align with current treatment pathway in the UK and the expected positioning of the product as follows:
		• SoC (background treatment with statins + ezetimibe): patients not eligible for PCSK9
		• BPA + ezetimibe: patients intolerant to statins
		• Inclisiran: ASCVD patients >2.6mol/l
		• Evolocumab:
		  ○ Primary prevention patients with HeFH and LDL-C >5.0 mmol/l
		  ○ High-risk ASCVD with LDL-C >4.0 mmol/l
		  ○ Very high-risk ASCVD and high-risk HeFH patients with LDL-C >3.5mmol/l
		Alirocumab: As per evolocumab
			Thank you for your comments and for providing additional detail on the treatment pathway. The comparators section aims to detail the range of potential treatments for the condition. Full details of the treatment pathway and positioning of the technologies with accompanying reference sources can be provided in the company’s submission for presentation to the committee.

Section	Consultee/ Commentator	Comments [sic]	Action
	HEART UK	Yes, but could also include icosapent ethyl - this is prescribed for those with CVD who are taking a statin to treat residual risk and is part of the current lipid management pathway. lipid-management-pathway-v7.pdf Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides (TA805)	Thank you for your comment. Icosapent ethyl has been added as a comparator. A reference to the lipid management pathway and TA805 has been added to the background section.
	Daiichi Sankyo	The comparators listed reflect NHS standard of care. However, bempedoic acid with ezetimibe is recommended for statin-intolerant patients (TA694), whilst obicetrapib has been studied in patients with maximally tolerated lipid modifying therapy. Robust clinical evidence should be presented by the company for efficacy/safety in a statin intolerant population to support any such recommendation in that subgroup.	Thank you for your comment. Statin intolerant populations were not excluded from the clinical trial. The committee will consider the evidence in order to make any recommendations.
	Novartis	Please note that inclisiran is a small interfering RNA (siRNA) therapy and not a PCSK9i, and therefore should not be included in the list for PCSK9i. Furthermore, please update the recommended population for inclisiran to "if there is a history of CV events ~~or~~ **AND** if LDLC is persistently 2.6mmol/l or more, despite maximally tolerated ~~lipid-lowering therapy~~ **statins with or without other lipid-lowering therapies or other lipid-lowering therapies when statins are not tolerated or contraindicated.**	Thank you for your comment. All mechanisms of action have now been removed from the scope. The recommendation

Section	Consultee/ Commentator	Comments [sic]	Action
			wording for inclisiran has been updated.
	Primary Care Cardiovascular Society	Are the comparators listed considered to be the standard treatments currently used in the NHS with which the technology should be compared? Have all relevant comparators been included? Yes	Thank you for your comment.
	UK Clinical Pharmacy Association	Are the comparators listed considered to be the standard treatments currently used in the NHS with which the technology should be compared? Have all relevant comparators been included? Yes	Thank you for your comment.
Outcomes	Menarini	A. Menarini Farmaceutica Internazionale SRL have no comment to add. We align with the list of proposed outcomes.	Thank you for your comment.
	HEART UK	Yes – see equality ongoing phase 3 trials i.e. PREVAIL CV outcomes trial pending.	Thank you for your comment. The scope includes a broad outcome for fatal or non-fatal cardiovascular events. Specific events from PREVAIL have now been added
	Daiichi Sankyo	N/A	N/A
	Novartis	N/A	N/A
	Primary Care Cardiovascular Society	Are the outcomes listed appropriate? Will these outcome measures capture the most important health related benefits (and harms) of the technology? Yes – CVD outcomes will be needed	Thank you for your comment. CVD outcomes are included.

Section	Consultee/ Commentator	Comments [sic]	Action
	UK Clinical Pharmacy Association	Currently follow the Heart UK recommendations around Lp(a). Does NICE need to include this advice? Suggest including triglycerides if looking at mixed dyslipidaemias.	Thank you for your comment. “Triglyceride level” has been included as an outcome. “Lipoprotein (a) level” was already included as an outcome in draft scope.
Equality	Menarini	A. Menarini Farmaceutica Internazionale SRL have no comment to add.	N/A
	HEART UK	This medication would be an additional treatment for those who may not meet the current criteria for prescription of medications such as PCSK9 inhibitors which require meeting specific LDL cholesterol targets/have existing CVD or icosapent ethyl which requires specific LDL/triglyceride levels, with existing CVD (and on statin) or those who do not meet criteria for adding in bempedoic acid which is indicated for those where statins are contraindicated/not tolerated. An additional “oral” medication which would be useful for those who may not want injectable treatments and what this entails in terms of storage/administration and/or who have needle phobias.	Thank you for your comments. The equalities issue raised here has been recorded in the equalities impact assessment. The committee will consider the potential equality issues raised during the appraisal process. Committee will consider the population and mode of administration in their decision making.
	Daiichi Sankyo	N/A	N/A
	Novartis	N/A	N/A

Section	Consultee/ Commentator	Comments [sic]	Action
	Primary Care Cardiovascular Society	Treatment to target for secondary prevention is mainly carried out in primary care. Limiting prescribing to secondary care will limit implementation as there is not the capacity on secondary care services.	Thank you for your comments. The equalities issue raised here has been recorded in the equalities impact assessment. The committee will consider the potential equality issues raised during the appraisal process. Whilst committee consider implementation, it is not within their remit for decision making.
	UK Clinical Pharmacy Association	No issues identified with these questions.	Thank you for your comment.
Other considerations	Menarini	A. Menarini Farmaceutica Internazionale SRL have no comment to add.	N/A
	HEART UK	NICE need to allow prescription medications that are not dangerous to be used in primary care. In reality, medicines may well be started in secondary care but NICE should not impose barriers to their prescription in primary care. NICE should align all their various therapy areas to the same levels and same access primary care.	Thank you for your comments. Please include details for committee consideration in the organisation submission. The technologies will be

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		NICE need a target low-density lipoprotein (LDL) cholesterol and non-HDL cholesterol for primary prevention, not a percentage reduction. HEART UK understands that obicetrapib also reduces lipoprotein (a), so this medication should be available to patients with raised lipoprotein (a). Given that lipoprotein (a) often is not measured and not available as a test to GPs, obicetrapib should be considered for any patient with an early cardiovascular event, irrespective of lipid level. This should be aligned to the HEART UK Lp(a) consensus statement: HEART UK consensus statement on Lipoprotein(a) A call to action	appraised in line with their marketing authorisations.
	Daiichi Sankyo	N/A	N/A
	Novartis	N/A	N/A
	Primary Care Cardiovascular Society	N/A	N/A
	UK Clinical Pharmacy Association	N/A	N/A
Questions for consultation	Menarini	Where do you consider obicetrapib and obicetrapib–ezetimibe will fit into the existing care pathway for primary hypercholesterolaemia or mixed dyslipidaemia? **We anticipate that Obicetrapib and Obicetrapib-ezetimibe will be positioned after ezetimibe in the treatment pathway for all patients.**	Thank you for your responses.

Section	Consultee/ Commentator	Comments [sic]	Action
		Would obicetrapib and obicetrapib–ezetimibe be used as add on treatments to all of the comparators listed in the draft scope? Or would they displace the use of any comparator? **Obicetrapib and Obicetrapib-ezetimibe would be given** • **When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C** • **When statins are contraindicated or not tolerated, and ezetimibe does not appropriately control LDL-C** **Except for SoC, Obicetrapib and Obicetrapib-ezetimibe would not be given as an add-on therapy, but would displace other listed comparators above.** Are all of the comparators listed in the draft scope used interchangeably or are any used in specific populations? **Inclisiran – restricted for use only in the secondary prevention (ASCVD) population based on reimbursement restrictions (LDL-C threshold)** **Bempedoic acid – restricted for use only in the statin intolerant population** **PCSK9i injectables – restricted for use only in secondary prevention (ASCVD) population in patients at high and very high CV risk, and in primary prevention HeFH where LDL-C is persistently >5mmol/l** Please select from the following, will obicetrapib and obicetrapib–ezetimibe be: **A. Prescribed in primary care with routine follow-up in primary care** **B. Prescribed in secondary care with routine follow-up in primary care**	

Section	Consultee/ Commentator	Comments [sic]	Action
		For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. **Bempedoic Acid – primary and secondary care prescription with primary care follow-up** **Inclisiran – primary and secondary care prescription with primary care follow-up** **PCSK9i – secondary care prescription only and secondary care follow-up** Would obicetrapib and obicetrapib–ezetimibe be candidates for managed access? **No** Do you consider that the use of obicetrapib or obicetrapib–ezetimibe can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? **As an oral lipid-lowering therapy, obicetrapib (alone or in combination with ezetimibe) may offer improved patient convenience and improved adherence; the full extent to which may not be fully measurable in the QALY calculations.** Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: ● could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatments will be licensed; ● could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by	

Section	Consultee/ Commentator	Comments [sic]	Action
		making it more difficult in practice for a specific group to access the technology; ● could have any adverse impact on people with a particular disability or disabilities. Obicetrapib and Obicetrapib-ezetimibe offer a safe and effective oral treatment option that is easily accessible across care settings, bridging the treatment gap for patients who remain above LDL-C thresholds despite maximally tolerated oral therapy and the more complex to access injectable therapies.	
	HEART UK	N/A	N/A
	Daiichi Sankyo	N/A	N/A
	Novartis	N/A	N/A
	Primary Care Cardiovascular Society	N/A	N/A
	UK Clinical Pharmacy Association	Could be considered over bempedoic acid as the reduction is bigger and the trials show obicetrapib reduces Lp(a) Add on to all treatments as works on a separate pathway. Happy with current comparators	Thank you for your responses.

Section	Consultee/ Commentator	Comments [sic]	Action
		Suggest “A” prescribing in primary care, to align with bempedoic acid, ezetimibe and statins to allow easier access to this treatment for patients. There are no special monitoring or treatment considerations that warrant secondary care prescribing or follow up.	
Additional comments on the draft scope	Menarini	No additional comment	N/A
	HEART UK	Clarify use for both primary and secondary prevention, as part of current lipid management pathway	Thank you for your comments, this has now been clarified in the “population” section of the scope.
	Daiichi Sankyo	N/A	N/A
	Novartis	N/A	N/A
	Primary Care Cardiovascular Society	N/A	N/A
	UK Clinical Pharmacy Association	N/A	N/A

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

Amgen

AstraZeneca

Genetic Alliance UK